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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/373,938	08/13/99	HALLENBECK	P

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EXAMINER	
BRUNOVSKIS, P	
ART UNIT	**PAPER NUMBER**
1632	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/373,938	Applicant(s) Hallenbeck et al.
	Examiner Peter Brunovskis	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Nov 24, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-33* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-33* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7 and 8*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The response filed 11/24/00 has been entered. Entry of new claims 32 and 33 is acknowledged. Claims 1-33 are pending in the instant application. Applicant's arguments filed 11/24/00 will only be considered to the extent that they apply to the pending claims; arguments directed to any other subject matter is considered moot.

Information Disclosure Statement

Reference CN 1216777 (Reference B2 in Paper No. 8, filed 9/11/00) was not considered, because no English translation was provided.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicants are required to comply with all of the requirements of 37 C.F.R. §§ 1.821 through 1.825. Any response to this Office Action which fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37

C.F.R. §§ 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Claim Objections

Claim 32 is objected to because of the following informalities: The period which follows "encoding endostatin" (line 1) should be replaced by a comma. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-27 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a tumor or metastases by direct intratumor administration of an adenoviral vector comprising a full length cDNA sequence encoding murine endostatin for expression of said endostatin, does not reasonably provide enablement for any and all methods of delivery in any and all hosts with an adenoviral vector comprising any and all DNA sequences encoding endostatin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments filed 11/24/00 have been fully considered but they are not persuasive. Applicants essentially argue that "[t]he Examiner...has not met her burden in showing that the specification does not provide an enabling disclosure" since "[t]he Examiner has provided no evidence, other than sheer speculation, which would indicate to those skilled in the art that adenoviral vectors including DNA sequences encoding endostatins other than murine endostatins could not be constructed, or that methods of administration other than direct intratumoral administration could not be employed". This argument is not persuasive because it essentially provides unsupported assertions that fail to rebut the prima facie case for lack of enablement set forth in the Office Action of 5/24/00. The previous Office Action set forth numerous grounds for rejection under lack of enablement. However, these arguments have not been specifically or sufficiently addressed by Applicants. For example, Applicants have failed to rebut the unpredictability in the art as it relates to adenovirus-mediated gene therapy or the points relating to the reference by Harris (Lancet) disclosing "that the receptors or targets are unknown and may not be expressed on human tumour vessels or to the same extent as in murine vessels" and that "these proteins are far from being ready for clinical use". The specification admits that "[t]he molecular mechanism of endostatin induced antiangiogenesis is not clear" (p. 2, last paragraph). In view of this uncertainty coupled with the uncertainties set forth by Harris, the Office has met its burden to provide evidence, other than sheer speculation, that would indicate to those skilled in the art that adenovirus vectors including DNA sequences encoding endostatins other than murine are not enabled by the instant disclosure.

It is further noted, that instead of rebutting the Office's specific grounds for lack of enablement as directed to methods of in vivo delivery, based on multiple references (e.g. Orkin et al., Miller et al., and Eck & Wilson etc.) highlighting problems and unpredictability in the art relating to systemic delivery of adenoviral-based gene therapy vectors and the unpredictability associated with extrapolating results in mice results to humans (e.g. Kerbel), Applicants merely assert (without arguing the specific arguments set forth in the references therein), and incorrectly characterize the evidence of record as indicating that "[t]he Examiner has provided no evidence, other than sheer speculation which would indicate to those skilled in the art that...methods of administration other than intratumoral administration could not be employed".

Since the response fails to rebut or address the specific grounds for lack of rejection set forth in the Office Action of 5/24/00, it fails to overcome the prima facie case for lack of enablement as directed to the rejected claims.

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for adenoviral vectors comprising DNA sequences operatively linked to promoters controlling the expression of endostatin or endostatin fusion proteins, does not reasonably provide enablement for vectors comprising DNA sequences lacking promoters or containing DNA sequences merely comprising DNA sequences encoding secretion signal peptide- and endostatin coding sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate

in scope with these claims, since it does not teach how to use adenoviral vectors of the above claims lacking operably linked promoters facilitating gene expression resulting in secretion of endostatin polypeptides.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-28 remain rejected and claim 33 is rejected under 35 U.S.C. 112, second paragraph, for the reasons set forth in the Office Action of 5/24/00, and for the reasons set forth below, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Note: Claims 5-10, 12, 13, 15-20, 22-27, and 29-31 were not listed in the preamble of the previous rejection, but they depend from the rejected claims as described in pp. 9-10 of the Office Action of 5/24/00 as acknowledged by Applicants on p. 8 of the response filed 11/24/00.

Claim 33 is indefinite in its recitation of the phrase "promoter controlling said DNA sequence" since it is not clear what metes and bounds apply to recitation of "controlling" in the context of the claim or what is actually being controlled. Changing the claim to --promoter controlling expression [or transcription] of said DNA sequence...-- would obviate the problem. Further, the claim is indefinite in its recitation of "RSV" since its is unclear what term "RSV" is abbreviating or what *specific* RSV promoter the claim is directed to (e.g. Respiratory Syncytial

Virus (RSV) contains multiple different promoters). Claim 33 is also indefinite because it is unclear how the RSV promoter controls the two independently recited sequences unless they are fused in-frame to one another. Changing the claim (or the claim to which it depends) to more accurately relate an operable linkage to the DNA sequence comprised of the two fused sequences in claim 33 would obviate the problem.

Applicant's arguments filed 11/24/00 have been fully considered but they are not persuasive. With regard to claims 4, 11, 14, 21, and 28, Applicants fail to obviate the grounds for rejection set forth in the Office Action of 5/24/00. Specifically, the rejected claims omit essential steps and are therefore incomplete claims lacking essential method steps that relate back to the preamble. MPEP 2111.02 notes that "[t]he preamble is not given the effect of a limitation unless it breathes life and meaning into the claim. In order to limit the claim, the preamble must be 'essential to point out the invention defined by the claim'". Applicants argue that "[o]ne of ordinary skill in the art would understand readily that if an adenoviral vector were administered to a host or to a cell, that upon administration, the adenoviral vector would be expected to express endostatin in the cell or in the host, and that if endostatin is expressed in the host, the endostatin in the cell or in the host may inhibit, prevent, or destroy the growth of tumors, such as colon cancer metastases, in the host. This argument is not persuasive since the preambles of the rejected claims fail to "breathe life and meaning into their claims". Claims 4, 11, 14, 21, and 28 are patentably indistinguishable, since they recite identical method steps that do not clearly relate back to each of the different and distinct preambles from which they depend.

With regard to claims 6, 13, 16, and 23, the response failed to rebut or address the specific grounds for indefiniteness as directed to recitation of "regionally". Consequently, the rejection stands.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 4-7, 11-17, 21-24, and 28-29 remain rejected under 35 U.S.C. 102(a) for the reasons set forth in the Office Action of 5/24/00, as being anticipated by Leboulch et al. (WO 99/264480).

Applicant's arguments filed 11/24/00 have been fully considered but they are not persuasive. Applicants concede that Leboulch discloses adenoviral vectors that contain endostatin sequences, but argue that "all actual examples in Leboulch are directed to retroviral vectors" and that "[o]ne skilled in the art is provided with no guidance regarding how to construct an adenoviral vector including a DNA sequence encoding endostatin" (p. 3). Leboulch, discloses the sequences of human and murine endostatin and explicitly claims delivery methods and composition comprising adenoviral vectors comprising DNA sequences encoding endostatin (e.g. cl. 18). Leboulch clearly anticipates the rejected subject matter and is not required to describe

construction of such vectors (or working examples comprising such), since construction of adenoviral vectors comprising transgenes was routinely performed in the art by those skilled in the art at the time the invention was made.

Claims 1-3 remain rejected under 35 U.S.C. 103(a) for the reasons set forth in the Office Action of 5/24/00, and for the reasons set forth below, as being unpatentable over Leboulch et al. (WO 99/264480) taken with Blezinger et al. (Nature Biotechnology, 17:343-348, 4/99).

Applicant's arguments filed 11/24/00 have been fully considered but they are not persuasive. Applicants argue that although "[t]he combination of Leboulch and Blezinger...at best enables one skilled in the art to construct a plasmid which includes a nucleic acid sequence encoding endostatin and a nucleic acid encoding a secretion signal from the mouse Ig-Kappa chain...[s]uch [a] combination provides no guidance and not even the remotest suggestion to one of ordinary skill in the art as to how to construct an adenoviral vector including a DNA sequence encoding endostatin as claimed by Applicants" (paragraph abridging pp. 4-5). Leboulch, discloses the sequences of human and murine endostatin and explicitly claims delivery methods and composition comprising adenoviral vectors comprising DNA sequences encoding endostatin (e.g. cl. 18). Leboulch clearly anticipates the rejected subject matter and is not required to describe construction of such vectors (or working examples comprising such), since construction of adenoviral vectors comprising transgenes was routinely performed in the art by those skilled in the art at the time the invention was made. Given that activity of endostatin requires its secretion into

the extracellular mileau and would require its coding sequences to be operatively linked to an exogenous secretion signal sequence, as suggested by Leboulch and Blezinger, it would require routine optimization to maximize expression in vivo or in vitro by combining the secretion signal sequence of Blezinger (i.e. Ig-kappa) in an adenoviral recombinant expressing endostatin. Constructing and designing such recombinants requires routine recombinant DNA methodologies routinely performed by those of ordinary skill in the art. Therefore, the invention as a whole was prima facie obvious at the time the invention was made.

Claims 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. and Blezinger et al. as applied to claims 1-3 above, and further in view of Lemarchand et al. (Circ. Res., 72(5):1132-1138, 5/93).

Leboulch and Blezinger were summarized above and in the Office Action of 5/24/00.

Additionally, Leboulch discloses AAV-based and nonviral plasmid-based comprising an RSV LTR (see e.g. Fig. 3). Leboulch does not explicitly disclose adenoviral vectors comprising a RSV promoter operatively linked to DNA sequences encoding a secretion signal sequence of Ig-kappa and a DNA sequence encoding endostatin.

Lemarchand et al. (and references therein) teach the use of recombinant adenoviral vectors expressing transgenes under the control of the RSV promoter for application in vascular biology studies (see e.g. last two paragraphs, pp. 1137-1138).

At the time the invention was made, it would have been obvious for one of ordinary skill in the art to combine the RSV LTR promoters of Leboulch or Lemarchand with the DNA sequences encoding a secretion signal sequence of Ig-kappa of Blezinger in the adenovirus-encoding endostatin embodiments of Leboulch, since a skilled artisan would have been motivated to optimize expression and secretion of endostatin when designing adenoviral vectors for use in vitro or in vivo uses, including vascular biology studies as described by Lemarchand. The skilled artisan would have been motivated to combine well-established constitutive promoter elements (such as RSV LTR) or secretion signal sequences (such as Ig-kappa) as taught by Leboulch, Lemarchand, or Blezinger, since these represent appropriate sequence elements known in the art for optimizing transgene expression performance, particularly in the context of the claimed subject matter. Therefore, the invention as a whole was prima facie obvious at the time the invention was made.

Claims 4, 7-10, 14, 18-21, and 25-27 remain rejected under 35 U.S.C. 103(a) for the reasons set forth in the Office Action of 5/24/00, and for the reasons set forth below, as being unpatentable over Leboulch et al. and Blezinger et al., as applied to claims 1-3 above, and further in view of O'Reilly et al. (U.S. 5,854,205).

Applicant's arguments filed 11/24/00 have been fully considered but they are not persuasive, since the arguments presented merely present an unsupported assertion "[that] the combination of O'Reilly with Leboulch and Blezinger would not even remotely suggest to one of

ordinary skill in the art an adenoviral vector including a DNA sequence encoding endostatin, and do not even remotely suggest to one of ordinary skill in the art that such a vector may be administered in an amount effective to provide expression of endostatin in an amount of up to 1,000,000 μg/ml, or at least 200 g/ml, or from about 200 g/ml to about 500 g/ml" (p. 6). It is noted that neither the instant specification, nor the claims provide any special guidance or recite any patentably distinct limitations distinguishing the methods of the instant invention over methods for adenoviral delivery in the prior art commensurate with the limitations recited in the method steps of the rejected claims, which are incomplete. Since the response fails to rebut or address the specific grounds or arguments for obviousness set forth in the Office Action of 5/24/00, it fails to overcome the prima facie case for lack of enablement as directed to the rejected claims.

Claims 28-31 remain rejected under 35 U.S.C. 103(a) for the reasons set forth in the Office Action of 5/24/00, and for the reasons set forth below, as being unpatentable over Leboulch et al. and Blezinger et al., as applied to claims 1-3 above, and further in view of Kovesdi et al. (U.S. 5,851,806).

Applicant's arguments filed 11/24/00 have been fully considered but they are not persuasive. Applicant's arguments filed 11/24/00 have been fully considered but they are not persuasive, since the arguments presented merely present unsupported inferences or assertions without addressing the specific grounds or arguments for obviousness set forth in the Office

Action of 5/24/00. For example, the response contends that "Kovesdi, however, does not disclose or even remotely suggest to one of ordinary skill in the art that the replication deficient vectors include a DNA sequence encoding endostatin" (sentence abridging pp. 6-7). In response to this argument directed individually against Kovesdi, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The response then proceeds to assert "[that] the combination of Leboulch, Blezinger, and Kovesdi, therefore, does not even remotely suggest to one of ordinary skill in the art Applicant's claimed method of expressing endostatin in a cell, such as a mammalian cell, such as A549 cells or Hep3B cells, by administering to a cell an adenoviral vector including a DNA sequence encoding endostatin" (p. 7, first full parargraph). However, Applicants fail to provide any support for this assertion, nor do they rebut or specifically address the specific grounds or arguments for obviousness set forth in the Office Action of 5/24/00 and have therefore failed to overcome the prima facie case for obviousness.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER